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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/801,157	03/07/2001	Hans-Peter Josel	RDID0089DUS	1582

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/801,157	JOSEL ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

3.00

DETAILED ACTION

Status of the Application

1. The Response filed April 6, 2005 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 1-32 were pending. Applicants canceled claims 1-32 and added claims 33-39. Therefore, claims 33-39 are pending.

4. Please note: Applicant's elected species (e.g., see 3/4/2004 Response) was not found in the art. Applicant is reminded of MPEP § 803.02 with respect to species elections:

> On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. ***The prior art search, however, will not be extended unnecessarily to cover all nonelected species***. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

5. Therefore, claims 33-39 are examined on the merits.

IDS

6. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action (e.g., 4/19/05 IDS).

Withdrawn Objections/Rejections

7. All previous rejections are withdrawn in view of Applicants' arguments and/or amendments.

New Rejections

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 33-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bredehorst et al. (Bredehorst, R.; Wemhoff, G. A.; Kusterbeck, A. W.; Charles, P. T.; Thompson, R. B.; Ligler, F. S.; Vogel, C.-V. "Novel Trifunctional Carrier Molecule for the Fluorescent Labeling of Haptens" *Analytical Biochemistry* **1991**, *192*, 272-279) and Brinkley (Brinkley, M. "A brief Survey of Methods for Preparing Protein Conjugates with Dyes, Haptens and Cross-linking Reagents" *Bioconjugate Chem.* **1992**, *3*, 2-13) and Merrifield (Merrifield, R. B. "Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide" *J. Am. Chem. Soc.* **1963**, *85*, 2149-2154) and Massey et al. (WO 87/067606) (Date of Patent is **November 5, 1987**).

For ***claim 33***, Bredehorst et al. (see entire document) teach a method for the synthesis of novel trifunctional carrier for the fluorescence labeling of haptens (e.g., see abstract), which reads on the claimed invention. For example, Bredehorst et al. teach the use of a linear peptide carrier (e.g., see Bredehorst, page 275, figure 1 showing "insulin" carrier). Bredehorst et al. introducing into the carrier 1-10 hapten molecules (e.g., see figure 1 wherein 2,4-dinitrophenol (DNP) is shown at the n-terminus; see also abstract). In addition, one alternative interpretation reads on the limitation wherein the haptens are attached to the carrier via an additional amino acid (e.g., in this scenario, the carrier is viewed as being the insulin A-chain without the N-terminal glycine, instead of the insulin A-chain in its entirety, and the additional amino acid is the N-glycine at the terminus). Bredehorst et al. also disclose adding 1-10 fluorescent marker molecules at defined distances (e.g., see figure 1 wherein three fluorescein molecules are disclosed; see also page 273, column 1, paragraph 1, "The sites for fluorophores attachment are 4, 17, and 21 amino acids away from the hapten attachment site"; see also page 277, column 2,

paragraph 1, The backbone of the carrier is the A-chain of insulin which provides several essential features, including ... (c) sufficient length between the label attachment sites to prevent self-quenching of the fluorophores, (d) sufficient length between the hapten and the label attachment sites to limit both interference by the fluorophores with antibody binding to the hapten and quenching of the fluorophores due to interaction with the hapten"). In addition, Bredehorst et al. disclose that the conjugate comprising a minimum of 5 and a maximum of 100 amino acids (e.g., see figure 1, DNP-Ins-Fl wherein 21 amino acids are disclosed). Finally, Bredehorst et al. disclose the use of "amino" groups for binding the haptens (e.g., the N-terminus) and fluorescein molecules (e.g., via a hydrazine linker) (e.g., see Bredehorst et al., figure 1; see also Methods section, especially page 273, column 1, Synthesis of DNP-Ins-FL section).

For ***claim 35***, Bredehorst et al. teach the use of an N-terminal primary amine to link the hapten to the carrier (e.g., see Bredehorst et al., figure 1).

The prior art teachings of Bredehorst et al. differ from the claimed invention as follows:

For ***claim 33***, Bredehorst et al. are deficient in that they **[1]** do not specifically teach the use of a method step for forming a linear carrier on a solid-phase (i.e., solid-phase synthesis). Bredehorst et al. purchased the insulin carrier from Sigma (see Bredehorst et al., page 273, column 1, last paragraph) and thus the reference is silent as to whether or not the insulin was produced via solid-phase synthesis, **[2]** do not use 1-10 additional amino acids as "linker" molecules for the attachment of metal chelates or, alternatively, the hapten molecule as well (see above). Bredehorst et al. only disclose, in

the alternative (see above), the use of amino acid linkers in conjunction with the hapten (e.g., see Bredehorst et al., figure 1 disclosing a Gly linker). Hydrazine linkers are used to attach the fluorescein molecules instead of amino acid side chains (e.g., see Bredehorst et al., figure 1). However, Bredehorst et al. do teach the use of lysine amino acids for the attachment of a fluorophores via the ε-NH_2 for the smaller DNP-Lys-Fl compound (e.g., Bredehorst et al., page 273, column 2, last paragraph; see also figure 1) and **[3]** do not use luminescent metal chelates as marker molecules. Bredehorst et al. use fluorescein markers instead (e.g., see Bredehorst et al., figure 1).

For ***claim 34 and 36-37***, Bredehorst et al. do not teach the use of "protecting groups" in conjunction with the reactive side groups.

For ***claims 38-39***, Bredehorst et al. do not teach the use of the haptens listed therein (e.g., see claims 38-39). Bredehorst et al. only teach the use of 2,4-dinitrophenol (e.g., see abstract).

However, the combined references of Brinkley, Merrifield and Massey et al. teach the following limitations that are deficient in Bredehorst et al.:

For ***claim 33***, the combined references of Brinkley, Merrifield and Massey et al. (see entire documents) teach **[1]** the use of solid-phase synthesis to make peptides like the insulin carrier disclosed by Bredehorst et al. (e.g., see Merrifield, abstract), **[2]** the use of amino acids linker molecules with reactive "amino groups" such as lysine for the attachment of haptens and fluorophores to a conjugate (e.g., Brinkley, section II.A.), and **[3]** the use of metal chelates for labeling haptens (e.g., see Massey et al., abstract, see also claim 11, "A method according to claim 1, wherein the reagent comprises an

electrochemiluminescent chemical moiety conjugated to an ... hapten ... or biotin"; see also claims 15-20 wherein bipyridine chelators are disclosed).

For ***claims 34 and 36-37***, the combined references of Brinkley, Merrifield and Massey et al. (see entire documents) teach the use of protecting groups (e.g., see Brinkley, page 2, column 2, paragraph 1, "in these molecules, the N-terminal amino group is N-acylated [i.e., protected]"; see also Merrifield, figure 1 showing examples of protecting groups like Cbzo). In addition, the protecting groups are disclosed as being selectively cleavable in basic conditions (e.g., see Merrifield, figure 1, last step wherein the Cbzo protecting group is cleaved by base i.e., NaOH).

For ***claim 35***, the combined references of Brinkley, Merrifield and Massey et al. (see entire documents) also teach the use of primary amines including the ε-amine of lysine (e.g., see Brinkley, page 2, column 1, last paragraph).

For ***claims 38-39***, the combined references of Brinkley, Merrifield and Massey et al. teach the use of hapten molecules like digoxin and theophyllin (e.g., see figures 6 and 7; see also Examples 32-34).

It would have been *prima facie* obvious to one skilled in the art at the time the invention to synthesize the peptide carrier molecule as disclosed by Bredehorst et al. on a solid-support as disclosed by Merrifield because Merrifield explicitly states that his solid phase synthesis technology is ideally suited for peptide synthesis, which would encompass the insulin peptide disclosed by Bredehorst et al. (e.g., see Merrifield, page 2149, column 1, paragraph 1). Furthermore, a person of skill in the art would have been motivated to use solid-phase synthesis technology disclosed by Merrifield to produce the

insulin disclosed by Bredehorst et al. because this technique overcomes prior difficulties with solubility and purification (e.g., see Merrifield, page 2149, column 1, paragraph 1). Finally, a person of skill in the art would reasonably have expected to be successful because the Merrifield peptide synthesis technique represents some of the most fundamental "classic" experiments in the art (for which Merrifield won the Nobel Prize in Chemistry "for his development of methodology for chemical synthesis on a solid matrix" in 1984) and has been routinely used and continuously improved upon for more than forty years (i.e., these techniques are not new and there is no unpredictability here). The Examiner also notes that thousands of references, if not tens of thousands, have been published since Merrifield's Nobel Prize work and are too numerous to list here.

Furthermore, it would have been *prima facie* obvious to substitute the metal chelates (e.g., see claims 15-20) disclosed by Massey et al. for the fluorescein molecules disclosed by Bredehorst et al. because Massey et al. explicitly state that these metal chelates can be used to label haptens, which would encompass the 2,4-dinitrophenol (DNP) hapten disclosed by Bredehorst et al. (e.g., see claim 11, "A method according to claim 1, wherein the reagent comprises an electrochemiluminescent chemical moiety conjugated to an ... hapten"). Furthermore, a person of skill in the art would have been motivated to use such metal chelates because Massey et al. explicitly states that their metal chelates are useful for immunoassays (e.g., see figures 1, 6 and 7; see also Summary of Invention; see also paragraph bridging pages 25-26), which would encompass the immunoassays disclosed by Bredehorst et al. (e.g., see Bredehorst et al., page 272, column 2, last paragraph). In addition, Massey et al. state that their metal

chelates are "highly diagnostic of the presence of a particular label, sensitive, non-hazardous, inexpensive, and can be used in a wide variety of applications" (e.g., see Massey et al., page 5, paragraph 1; see also Examples 36 and 37). Finally, a person of skill in the art would have reasonably expected to be successful because Massey et al. state that their metal chelates "can be used in a wide variety of applications" (e.g., see Massey et al., page 5, paragraph 1) wherein the labeling of haptens represents a "preferred embodiment" (e.g., see Massey et al., claim 11; see also figures 1, 6 and 7; see also Examples; see also page 7). Massey et al. also state, "Extensive work has been reported on methods for detecting Ru(2,2'-bipyridine)$_3^{2+}$ using photoluminescent, chemiluminescent, and electrochemiluminescent means", which shows that the art is not new and unpredictable (e.g., see Massey et al., page 7, last paragraph; see also page 32, lines 26-29 wherein Massey explicitly state that said metal chelates can be conjugated to haptens, "In one embodiment of the invention the reagent is a electrochemiluminescent chemical moiety conjugated to an ... hapten").

In addition, it would have been *prima facie* obvious at the time the invention was made to use amino acid linkers, such as lysine, to attach the metal chelating groups disclosed by Massey et al. to the carrier peptide as disclosed by Bredehorst et al. because the method of attachment represents a mere design choice that was well known in the art (e.g., see Brinkley, entire document, reviewing various methods that were "standard" in the art for attaching haptens and/or labels to a carrier; see especially section II.A. wherein the use of lysine "handles" are disclosed). Furthermore, Brinkley explicitly state that amine-probes like lysine can be used to attach haptens like the DNP disclosed by

Bredehorst et al. (e.g., see Brinkley, page 10, column 1, paragraph 2, "The following general procedure is ... adaptable to amine-reactive ... hapten"). A person of skill in the art would have been motivated to use lysine as linker for the attachment of the haptens and/or metal chelates because said lysine can be easily incorporated into a peptide and/or protein through synthesis and/or genetic manipulation (e.g., Brinkley, page 2, column 1, last full paragraph) and are "... reasonably good nucleophiles ... and therefore react easily and cleanly with a variety of reagents to form stable bonds" (e.g., see Brinkley, page 2, last paragraph). Finally, a person of skill in the art would have reasonably expected to be successful because Brinkley state that the ε-amine of lysine is "one of the most common" reactive groups employed to link haptens and/or marker molecules to a protein conjugate (e.g., see Brinkley, page 2, last paragraph). In addition, Bredehorst et al. explicitly show that a hapten like 2,4-dintrophenol (DNP) can be linked to a marker molecule using lysine (e.g., see figure 1, compound DNP-Lys-Fl; see also page 278, column 1, first full paragraph, "In principle, labeling of a hapten with multiple fluorophores is fairly simple. Polyamines such as polylysine ... are suitable").

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
June 23, 2005

BENNETT CELSA
PRIMARY EXAMINER